REMARKS

The Pending Claims

Claims 1, 2, 5, 8, 18 and 20-21 are pending after the claim amendments herein and under active consideration. The pending claims are directed to plasmids comprising tightly regulated promoters operatively linked to an isolated and purified PAL DNA sequences.

The Office Action

Claims 1-8 and 18-22 are rejected.

Claims 1-8 and 18-22 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 18-22 are rejected under 35 U.S.C. § 112, first paragraph as containing new matter and therefore failing to comply with the written description requirement.

Claims 1-8 and 18-22 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Guzman et al. (Journal of Bacteriology, 177(14):4121-4130, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996).

Claims 1-3, 6, 8, 18 and 21 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996).

Claims 7 and 20 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996),

and further in view of Novagen Inc. allegedly admitted prior art (Specification page 15, line 34).

Amendments

Claims 1, 5, 18 and 20 are currently amended. Claims 3, 4, 6, 7, 9-17, 19 and 22 are canceled. The amendments to the claims do not introduce new matter; and are fully supported by the specification, as originally filed. Amendment of the claims is made without prejudice and without intent to abandon any originally claimed subject matter.

Rejection Under 35 U.S.C. § 112, 2nd paragraph

Claims 1-8 and 18-22 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendment and the following remarks, Applicants believe this rejection has been rendered moot.

According to the Office Action, the term "leaky" is a term of degree, which does not have a specific basis for comparison in the claims and therefore renders the claims indefinite. While Applicants respectfully disagree, in order to expedite prosecution, the term "leaky" has been removed from the claims. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 112, 1st paragraph

Claims 1-8 and 18-22 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing new matter and therefore failing to comply with the written description requirement. In view of the amendment and the following remarks, Applicants believe this rejection has been rendered moot.

According to the Office Action, the newly created subgenus of "leaky regulated promoters" changes the scope of the disclosure and is therefore new matter. While Applicants respectfully disagree, in order to expedite prosecution, the term "leaky regulated promoters" has been removed from the claims. Accordingly, withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

I. Claims 1-8 and 18-22 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988) relied upon only for the description of P6, Guzman et al. (Journal of Bacteriology, 177(14):4121-4130, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996). Applicants respectfully traverse this rejection.

According to the Office Action, while Anilionis fails to teach a plasmid with PBOMP-1 and a tightly regulated promoter, such as the arabinose inducible promoter or T7 promoter, Anilionis does teach that "it is desirable to use strong promoters in order to obtain a high level of transcription..." Page 5, 1st paragraph. Makrides et al allegedly teach that it is desirable to use strong, tightly-regulated inducible promoters in order to obtain a high level of transcription and the vectors in Guzman et al meet these criteria. Page 6, 2nd paragraph.

However, according to Guzman, "[w]hile maximum [expression] levels [obtained by their arabinose inducible promoter] are high enough to permit most studies that require overproduction, they are not as high as those obtained from strong inducible promoters..." Page 4129, lines 38-43. Accordingly, Guzman does not characterize the arabinose inducible promoter as a strong inducible promoter.

This is because Guzman is concerned with the production of proteins for the study/experimentation of gene mutations (*citing* Guzman, pg. 4128, 2nd column, 4th paragraph: "[t]he tight control of expression provided by the araC-P_{BAD} promoter... has been indespensible in the isolation and study of null mutations... since leakiness can obscure results."). Guzman utilizes the arabinose inducible-promoter as a research tool, not in production of a vaccine or medicament as provided by Anilionis.

On the contrary, Anilionis does use strong promoters and obtains high levels of transcription for the purposes of vaccine or medicament production (albeit with reduced lipidation). *See* Examples, pages 43-120. Accordingly,

attributes asserted by the Office Action for selecting a desirable promoter would lead one to select Anilionis' promoter, not those in Guzman or the present claims.

The U.S. Supreme Court recently clarified the legal standard of obviousness, citing text from an earlier opinion: "[u]nder § 103, scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." KSR Intern. Co. v. Teleflex Inc., U.S. 2007 (2007 WL 1237837 (U.S.), at 6, citing *Graham v. John Deere Co. of Kansas City*, 86 S.Ct. 684.

Regarding a motivation to combine prior art references, the Supreme Court stated that an Examiner's analysis must be made explicit. Id. at 13. Furthermore, the Supreme Court noted that it can be important to identify a reason to combine elements from different references. Id. The Supreme Court warned that "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." Id. at 16, citing Graham, 393 U.S., at 36. Furthermore, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" Id.

Irrespective of the prior existence of arabinose promoters, neither Guzman nor Makrides provide any reason to modify Anilionis' promoters. The only basis on which that argument can be founded involves legally-improper hindsight reconstruction of the present claims. Accordingly, withdrawal of the rejection is respectfully requested.

II. Claims 1-3, 6, 8, 18 and 21 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988) relied upon only for

description of P6, Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996).

According to the Office Action, "Makrides et al teach that is [sic] desirable to use strong, tightly-regulated, inducible promoters in order to obtain a high level transcription and the vectors of Mertens et al meet these criteria and Mertens et al teach that the PT7 containing vectors have the potential to considerably improve the expression level of other heterologous genes." Page 9, 1st paragraph.

Makrides is concerned with tight regulation due to the potential toxicity of expressed proteins on the host cell (page 513, 2nd column and page 514, 2nd column, lines 7-9). Mertens describes "a versatile dual-promoter expression plasmid for heterologous gene expression in *Escherichia coli* which contains both λ_{PL} and P_{T7} promoters." Abstract. According to Mertens, "[g]enes placed under [only] T7 promoter control and which code for potentially toxic protein were difficult or impossible to maintain in such expression systems." Mertens et al., Biotechnology v. 13 (1995) pg 175-179 (at page 175 2nd paragraph). Accordingly, Mertens in conjunction with Makrides teach away from the use of T7 promoter without the λ_{PL} promoter.

As amended, claims 1-3 and 8, pertain to arabinose inducible promoters. Claims 18 and 21 are directed to a promoter consisting of a T7 promoter. Thus Mertens and Makrides, which suggest a dual λ_{PL} and P_{T7} promoter system are describing a different promoter system from what is being claimed. Accordingly, Applicants respectfully request withdrawal of the rejection.

III. Claims 7 and 20 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Anilionis et al. (WO 90/02557) in view of Nelson et al. (Infection and Immunity, 56(1):128-134, 1988), Mertens et al. (Gene, 164:9-15, 1995) and Makrides et al. (Microbiology Reviews, 60(3):512-538, Sept. 1996), and further in view of Novagen Inc. allegedly admitted prior art (Specification page 15, line 34).

Claim 7 is canceled, thus this rejection only applies to claim 20. As described above, Anilionis, Nelson, Mertens and Makrides describe a different promoter system than what is being claimed. Novagen is relied upon solely for the description of a plasmid designated pPX4019. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants would like to thank the Examiner for her thorough review of this application. In view of the amendments and remarks, it is submitted that the application is now in condition for allowance. Early notice to that effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (973) 660-6615.

Respectfully submitted,

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